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HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
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OFFICE OF PREVENTION, PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

Date: June 23, 2009

SUBJECT: DINOTEFURAN: Review of Draft Protocol for a Developmental Neurotoxicity Study

PC Code: 044312
Decision No.: 407140
Petition No.: NA
Risk Assessment Type: NA
TXR No: 0055184
MRID No.: 47677501, 47677502

DP Barcode: D364521, D366688
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Health Effects Division (7509P)

THROUGH: Jess Rowland, Chair
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I. CONCLUSIONS

After evaluating the available relevant data on dinotefuran, the Health Effects Division's DNT Work Group arrived at the following conclusions:

(1) The Group concurred with the dose levels proposed by the Registrant (0, 1000, 3000, or 10,000 ppm) for the main developmental neurotoxicity study, based on the results of and range finding study (MRID 47677501).

(2) It is unnecessary to employ direct pup dosing in the main DNT study, based on the results of a milk transfer study in lactating rats (MRID 47013402; TXR 0054576);

(3) Evaluation of immunotoxicity parameters are not needed in the main developmental neurotoxicity study, based on the results that no immunotoxicity was found at the limit dose (1053 mg/kg) in the dose range finding study which had tested all the parameters required in a developmental immunotoxicity study

II. ACTION REQUESTED

Review registrant's protocol (MRID 47677502) for the main developmental neurotoxicity (DNT) study and the rationale provided for not employing direct pup dosing and not including evaluation of immunotoxicity parameters in the main DNT.

III. BACKGROUND

The registrant has been required to perform a DNT study and a developmental immunotoxicity study. To fulfill the requirement, the registrant in this submission provide the results of an Oral (Diet) Dosage Range Finding Developmental Neurotoxicity and Developmental Immunotoxicity Study of MIT-446 (Dinotefuran) in CRL:CD(SD) Rats (MRID 47677501). The registrant also submitted two documents: (1) Rationale for not Including Immunotoxicity Endpoints in the Main Developmental Neurotoxicity Study of MTI-466 (Dinoteturan) in CRL:CD(SD) Rats and (2) Rationale for not Employing Direct Pup Dosing in a DNT Study.

IV. RESULTS/DISCUSSION

On June 18, 2009, the Health Effect Division's DNT Work Group reviewed the Draft Data Evaluation Record of the range finding study and the rationales submitted by the registrant.

In the range finding DNT/DIT study (MRID No. 47677501), groups of presumed pregnant Sprague Dawley rats (10/dose) were administered Dinotefuran in the diet at 0, 1000, 3000, or 10,000 ppm (equivalent to 105, 318, 1035 mg/kg/day) beginning on gestation day (GD) 6 through lactation day (LD) 21. The dams were allowed to litter normally, and 20 F1 pups/sex/dose group were fed the same dietary concentrations as their dams beginning on PND 21 until termination. Thus, in this dose range finding DNT/DIT study the F1 generation progeny were potentially exposed continuously during gestation from day 6, throughout lactation and for 5 weeks following weaning. Systemic toxicity parameters were evaluated in the P and F1 generations. At the end of the F1 generation exposure period 10 rats/sex/group (from 9 or 10 litters/group) were subjected to phenotypic analysis of splenocyte subpopulations and an evaluation of innate immunity in the natural killer(NK) cell assay using YAC-1 tumor cells. Another set of 10 rats/sex/group were subjected to an evaluation of humoral immunity using the IgM antibody-forming cell response to a T-cell-dependent antigen (sheep erythrocytes) (TXR No. 0055184).

No maternal toxicity was seen at any dose. **The maternal NOAEL was 10,000 ppm (1035.4 mg/kg/day); a maternal LOAEL was not established. The offspring LOAEL was 10,000 ppm (1035.4 mg/kg/day) based on consistent decrease in body weights in both sexes from PND 22-57; the offspring NOAEL was 3000 ppm (317.8 mg/kg/day).**

There was no evidence of immunotoxicity. There were no effects on the innate or humoral components of the immune system. No differences attributable to treatment were noted in the distribution of splenocyte subpopulations. Spleen weights were unaffected by treatment. **The immunotoxicity NOAEL was 10,000 ppm (1035.4 mg/kg/day); a LOAEL was not established.**

Based on the lack of evidence for immunotoxicity in this study where a biologically meaningful number of litters per group (9 or 10) and three distinct immunological endpoints were employed, the Agency concurred with the registrant's request for not including immunotoxicity endpoints in the main DNT study.

In the milk transfer study (MRID 47013402), Sprague Dawley rats received oral gavage doses of 50 or 500 mg/kg, the expected dose range in the DNT, on lactation days (LD) 2, 4, 8, and 12. Whole blood, plasma and milk were assayed for radioactivity 0.5 and 1.5 hours, or 2 and 4 hours after treatment at 50 or 500 mg/kg, respectively. A rapid transfer of orally absorbed dinotefuran associated radioactivity into the milk of lactating rats was demonstrated. At both doses, concentrations in milk were consistently higher than those in whole blood or plasma from LD 2 to LD 12; approximately 100% higher at 50 mg/kg/day and 60% higher at 500 mg/kg/day. The data also showed that the extent of transfer into maternal milk was not influenced by the day of lactation since the milk, blood and plasma concentrations remained essentially constant from LD 2 to LD12. These data demonstrated both *in utero* and post-natal exposure of the developing rat since the suckling pups will be exposed to dinotefuran in the milk when maternal animals are treated orally during gestation and lactation.

Based on the results of the range finding and milk transfer studies, and consideration of the rationale provided by the registrant, the DNT Work Group concluded that there is no need for direct pup dosing in the DNT study because the data showed that dinotefuran was present in milk of treated lactating rats and in the fetal blood and organs examined (brain, heart, kidneys, liver, and lungs). Based on the results that no immunotoxicity was found at 10,000 ppm (1053 mg/kg) in the dose range finding study which had tested all the parameters required in a developmental immunotoxicity study, the immunotoxicity endpoints are not need in the main DNT study. The DNT Work Group also recommended that the doses of 100, 300, and 1000 mg/kg be employed for the developmental neurotoxicity study.

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